A Randomized, 2-period, 2-treatment, Single-dose, Crossover Study to Assess the Bioequivalence of the Fixed Dose Combination (FDC) of Dapagliflozin 10 mg and Sitagliptin 100 mg, and Dapagliflozin 10 mg and Sitagliptin 100 mg Administered as Individual Tablets in Healthy Subjects

CSR Synopsis: 06 October 2022

2 SYNOPSIS

Title of Study:	A Randomized, 2-period, 2-treatment, Single-dose, Crossover Study to Assess the Bioequivalence of the Fixed Dose Combination (FDC) of Dapagliflozin 10 mg and Sitagliptin 100 mg, and Dapagliflozin 10 mg and Sitagliptin 100 mg Administered as Individual Tablets in Healthy Subjects	
Study Numbers:	Parexel Study No.: CCI Sponsor Study No.: D1683C00014	
Investigational Medicinal Products (IMP):	Test Product: Dapagliflozin/sitagliptin 10 mg/100 mg FDC film-coated tablet Reference Product: Dapagliflozin 10 mg film-coated tablet and sitagliptin 100 mg film-coated tablet as individual tablets	
Indication Studied:	Type 2 Diabetes Mellitus	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	Dr. med. Rainard Fuhr	
Study Center:	Parexel Early Phase Clinical Unit, Berlin	
Publication:	None	
Study Duration:	First subject first visit: 21 Mar 2022	Last subject last visit: 31 May 2022

Study Objective(s):

Primary objective:

To demonstrate the fasted state bioequivalence between a dapagliflozin/sitagliptin 10 mg/100 mg FDC tablet relative to dapagliflozin 10 mg + sitagliptin 100 mg when co-administered as individual tablets in healthy subjects.

Secondary objective(s):

- To characterize the pharmacokinetic (PK) profiles of a dapagliflozin/sitagliptin 10 mg/100 mg FDC tablet and dapagliflozin 10 mg + sitagliptin 100 mg when co-administered as individual tablets in healthy subjects in a fasted state.
- To assess the safety and tolerability of single doses of a dapagliflozin/sitagliptin 10 mg/100 mg FDC tablet and dapagliflozin 10 mg + sitagliptin 100 mg when co-administered as individual tablets in healthy subjects.

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Study Design:

This study was a randomized, open-label, 2-period, 2-treatment, single-dose, crossover study in healthy subjects (males and females), performed at a single study center.

The study comprised:

- A Screening Period of maximum 28 days.
- Two Treatment Periods during which subjects were resident at the Clinical Unit from the day before dosing (Day -1) with Treatment A (test formulation) or B (reference formulation) until at least 72 hours after dosing for collection of PK samples; subjects were discharged on the morning of Day 4. Each Treatment Period was separated by a washout period of minimum 7 days, maximum 14 days.
- A final Safety Follow-up Visit 7 to 14 days after the last dosing with the IMP (Treatment A or B).

All subjects were randomized to receive a single dose of the following treatments after an overnight fast of 10 hours:

- Treatment A: 1 × dapagliflozin/sitagliptin 10 mg/100 mg FDC tablet (test formulation).
- Treatment B: 1 × dapagliflozin 10 mg tablet + 1 × sitagliptin 100 mg tablet co-administered as individual tablets (reference formulation).

Subjects were randomized 1:1 to one of 2 treatment sequences: Treatment A followed by Treatment B or Treatment B followed by Treatment A.

Study Subjects:

Planned for Inclusion:	**Randomized:**	**Completed Study:**
44 subjects	46 subjects	43 subjects

Main Inclusion Criteria:

Healthy male and female subjects (of non-childbearing potential or using acceptable measure of birth control as per standard criteria), 18 to 55 years of age (inclusive), with a body mass index (BMI) between 18.5 to 30 kg/m^2 inclusive, and weighed at least 50 kg and no more than 100 kg inclusive. All subjects provided signed and dated written informed consent prior to any study specific procedures.

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Investigational Medicinal Product(s):

Treatment Name	Treatment A	Treatment B	
Intervention name	Dapagliflozin/sitagliptin FDC	Dapagliflozin (FORXIGA™) [a]	Sitagliptin (JANUVIA™)
Type	Drug	Drug	Drug
Dose formulation	Film-coated tablet	Film-coated tablet	Film-coated tablet
Unit dose strength	10 mg/100 mg	10 mg	100 mg
Dosage levels	10 mg/100 mg, single dose	10 mg single dose	100 mg single dose
Route of administration	Oral	Oral	Oral
Use	Experimental – active test product	Active-reference product	Active-reference product
IMP	IMP	IMP	IMP
Supplier	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.
Packaging and labeling	Study Intervention was provided in blister packs. Each blister pack was labeled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Study Intervention was provided in blister packs. Each blister pack was labeled in accordance with GMP Annex 13 and per country regulatory requirement.	Study Intervention was provided in blister packs. Each blister pack was labeled in accordance with GMP Annex 13 and per country regulatory requirement.
Batch/Manufacturing Lot Number	CCI	CCI	CCI
Expiry Date	CCI	CCI	CCI

[a] FORXIGA™ (dapagliflozin) is a trademark of the AstraZeneca group of companies.
[b] JANUVIA™ (sitagliptin) is trademark of the Merck Sharp & Dohme Corp group of companies.

Duration of Treatment:

Subjects were involved in the study for up to 10 weeks, excluding subjects who withdrew from the study.

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Treatment Compliance:

Dosing took place at Parexel Early Phase Clinical Unit. Administration of study intervention was recorded in ClinBase™. Compliance was assured by direct supervision and witnessing of study intervention administration. After administration, a check of the subject's mouth and hands was performed.

Variables for Evaluation:

Pharmacokinetic Parameters:

- Primary PK parameters: AUCinf, AUClast, and Cmax.
- Secondary PK parameters: tmax, t1/2λz, MRTinf, λz, CL/F, and Vz/F.

Safety Variables:

- Adverse events (AEs).
- Vital signs (systolic and diastolic blood pressure [BP], pulse rate and tympanic temperature).
- 12-Lead electrocardiograms (ECGs).
- Physical examination.
- Clinical laboratory assessments (hematology, coagulation, clinical chemistry, and urinalysis).

Statistical Methods:

Analysis populations:

- The randomized set consisted of all subjects randomized into the study.
- The safety analysis set consisted of all subjects who received at least 1 dose of Treatment A or Treatment B and for whom any safety post-dose data were available.
- The PK analysis set consisted of all subjects in the safety analysis set for whom at least 1 of the primary PK parameters for dapagliflozin and sitagliptin could be calculated for at least 1-treatment period, and who had no important protocol deviations thought to impact on the analysis of the PK data.
- The bioequivalence analysis set was defined as the subset of the PK analysis set consisting of subjects for whom at least 1 of the primary PK parameters for dapagliflozin and sitagliptin can be calculated for 2 treatment periods.

Presentation and Analysis of Pharmacokinetic Data:

Listings of PK blood sample collection times, as well as derived sampling time deviations were provided. Plasma concentrations and PK parameters were summarized by treatment using appropriate descriptive statistics. Where possible, the following descriptive statistics were presented: n, arithmetic mean, standard deviation (SD), geometric mean (gmean), gmean - gSD, gmean + gSD, geometric coefficient of variation (gCV%), median, minimum, and maximum. For tmax, only n, median, minimum, and maximum were presented.

Individual plasma concentrations versus actual time were plotted in linear and semi-logarithmic scale with all treatments overlaid on the same plot and separate plots for each subject.

Combined individual plasma concentration versus actual times were plotted in linear and semi-logarithmic scale (separate plots for each treatment).

Geometric mean plasma concentration (±gSD) versus nominal sampling time were plotted in linear and semi-logarithmic (no gSD presented) scale with all treatments overlaid on the same figure.

Bioequivalence was assessed between Reference Treatment B and Test Treatment A based on the bioequivalence analysis set. Analyses were performed for all subjects with an evaluable parameter in both study periods using a random effects analysis of variance (ANOVA) model using the natural logarithm of AUCinf, AUClast and Cmax as the response variables, fixed effects terms for sequence, period, and treatment, and random effects for subject nested within sequence. Transformed back from the logarithmic scale, geometric means together with confidence intervals (CIs) (2 sided 95%) for AUCinf, AUClast, and Cmax were calculated and presented. Also, ratios of geometric means together with CIs (2 sided 90%) were estimated and presented. Additionally, the 90% CIs for the differences in tmax were calculated (using Hodges-Lehman estimator) and presented.

If the 90% CIs for the geometric mean ratios for AUCinf (AUClast for some agencies) and Cmax were entirely contained within 0.8000 and 1.2500, it would be concluded that the 2 formulations are bioequivalent.

Presentation and Analysis of Safety Data:

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarized using descriptive statistics (n, mean, SD, min, median, max) by treatment. Categorical variables were summarized in frequency tables (frequency and proportion) by treatment group. The analysis of the safety variables was based on the safety analysis set.

Adverse events were summarized by preferred term (PT) and system organ class (SOC) using the most recent Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 25.0. Furthermore, listings of adverse events leading to permanent IMP discontinuation (DAEs) were made and the number of subjects who had any AEs, DAEs and AEs with severe intensity was summarized.

Tabulations and listings of data for vital signs, clinical laboratory tests, and ECG were presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment was reported as an AE. Data were summarized for the observed values at each scheduled

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assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline was defined. Clinical laboratory data were reported in international units.

Determination of Sample Size:

If there was no difference in the bioavailability of dapagliflozin 10 mg when administered in FDC tablets and the bioavailability of dapagliflozin 10 mg when co-administered with sitagliptin 100 mg in the fasted state, then 44 subjects (22 per randomized sequence) would provide > 99%, 98.7%, and 98.6% statistical power to conclude bioequivalence with respect to dapagliflozin Cmax, AUCinf, and AUClast, respectively. If there was a 5% difference, then 44 subjects would provide > 99%, 90.2%, and 90.6% statistical power to conclude bioequivalence with respect to dapagliflozin Cmax, AUCinf, and AUClast, respectively.

If there was no difference in the bioavailability of sitagliptin 100 mg when administered in FDC tablets and the bioavailability of sitagliptin 100 mg when co-administered with dapagliflozin 10 mg in the fasted state, then 44 subjects would provide > 99%, 98.5%, and > 99% statistical power to conclude bioequivalence with respect to sitagliptin Cmax, AUCinf, and AUClast, respectively. If there was a 5% difference, then 44 subjects would provide 92.2%, 90.2%, and 90.6% statistical power to conclude bioequivalence with respect to sitagliptin Cmax, AUCinf, and AUClast, respectively.

Overall, if there was no difference in bioequivalence between the FDC tablets and the co-administered tablets within each cohort, then 44 subjects (22 per sequence) would provide 98.5% power to conclude bioequivalence with respect to Cmax, AUCinf, and AUClast for both dapagliflozin and sitagliptin. The overall power would be 90.2% if there was a 5% difference in bioequivalence. CCI

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Protocol Deviations:

One important protocol deviation was reported for subject PPD who was enrolled despite not qualifying for eligibility according to exclusion criterion 15. PPD

Pharmacokinetic Results:

Geometric mean ratios and corresponding 90% CIs of dapagliflozin were 98.77% (96.87, 100.71%), 99.49% (97.50, 101.51%) and 96.96% (90.57, 103.81%) for AUCinf, AUClast and Cmax, respectively. For sitagliptin, they were 99.74% (98.25, 101.26%), 99.85% (98.33, 101.40%) and 100.12% (94.51, 106.07%) for AUCinf, AUClast and Cmax, respectively. Geometric mean ratios and corresponding 90% CIs for all primary PK parameters of dapagliflozin and sitagliptin were contained well within the bioequivalence limit of 0.8000 and 1.2500, demonstrating that bioequivalence was achieved between dapagliflozin/sitagliptin 10 mg/100 mg FDC tablet and dapagliflozin 10 mg + sitagliptin 100 mg co-administered individual tablets.

Between-subject variability (gCV%) in PK exposures was up to approximately 30% and 25% for dapagliflozin Cmax and AUCs, respectively, and up to approximately 32% and 20% for sitagliptin Cmax and AUCs, respectively, and similar between treatments.

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Safety Results:

- In total, 20 subjects (43.5%) experienced 33 AEs during the study, with AEs occurring in a comparable number of subjects after Treatment A and Treatment B.
- There was 1 severe AE, 2 moderate AEs, and the remaining AEs were all mild in intensity.
- For 15 of the 46 randomized subjects (32.6%), AEs were assessed by the investigator as possibly related to the IMP. All possibly related events were of mild intensity except 2 AEs of moderate headache, and all resolved.
- There were no death or other SAEs reported during the study.
- Three subjects had AEs leading to permanent IMP discontinuation: 1 subject reported COVID-19 infection, 1 subject was discontinued due to a severe AE of Panic attack PPD , and 1 subject reported an event of Rash which was assessed as related to the IMP. All 3 subjects were withdrawn from the study.
- The SOCs with the highest incidence rate of AEs were Nervous System Disorders (21.7% of subjects), and Infections and infestations (13.0% of subjects).
- The most frequently reported AEs were headache (9 [19.6%] subjects), nausea (3 [6.5%] subjects), and rash and urinary tract infection, each event reported in 2 (4.3%) subjects.
- No clinically significant changes in clinical laboratory results (hematology, clinical chemistry, coagulation, and urinalysis), vital signs (systolic and diastolic BP, pulse rate, tympanic temperature) or 12-lead safety ECG data were observed. No AEs associated with abnormal clinical results were reported.
- None of the reported AEs were likely to have an effect on PK.

Conclusion:

- Bioequivalence was achieved between dapagliflozin/sitagliptin 10 mg/100 mg FDC tablet and dapagliflozin 10 mg + sitagliptin 100 mg co-administered individual tablets, based on the statistically equivalent PK exposures for dapagliflozin and sitagliptin observed following oral administration of FDC tablet and co-administered individual tablets under fasted state.
- Dapagliflozin and sitagliptin were well tolerated in healthy subjects when administered as a FDC tablet or as individual tablets, and no new safety signals were identified.
- The COVID-19 pandemic was not judged to meaningfully impact overall quality of the study, including conduct, data and interpretation of results.

Version and Date of Report: Version 1.0, dated 06 Oct 2022

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.